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How to
prevent
and manage

Tumor lysis syndrome

Patients undergoing cancer treatment are at risk for this life-threatening complication. Here's the latest information about recognizing signs and symptoms, managing the syndrome, and preventing future episodes.

By Jeanne Held-Warmkessel,
MSN, RN, AOCN, ACNS-BC



POTENTIALLY FATAL, tumor lysis syndrome (TLS) is a metabolic disturbance caused by the death of cancer cells during cancer treatment and the release of their intracellular components into the bloodstream. It's characterized by the rapid development of hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia. Risk factors for TLS include a large tumor size, tumors with rapid cell division and growth, hematologic cancers such as acute leukemia or high-grade (aggressive) lymphoma, and tumors with a high sensitivity to chemotherapy.^{1,2} Patients with high lactate dehydrogenase levels (greater than 1,000 U/L) and impaired renal function are also at risk, as are some patients with mediastinal tumors.³ Several chemotherapy agents, including cytarabine, cisplatin, etoposide, and paclitaxel, are associated with TLS.

Based on the presence of certain risk factors, patients can be placed into low-, intermediate-, or high-risk categories.

- High-risk patients are those with Burkitt lymphoma, lymphoblastic lymphoma, or B-cell acute lymphoblastic leukemia.
- Patients at intermediate risk have diffuse large-cell lymphoma or another type of rapidly growing cancer.
- Low-risk patients have indolent (slow-growing) lymphoma or another slowly proliferating cancer.¹

When TLS is present, it's diagnosed by lab tests or clinical signs and symptoms. Used to classify and grade TLS, the Cairo-Bishop Grading System defines lab abnormalities in serum uric acid, potassium, and phosphorus levels as a 25% increase over baseline and a 25% decrease from baseline in serum calcium levels. This system considers lab value changes that occur in patients from 3 days before to 7 days after chemotherapy begins. The clinical abnormalities classified by this system are graded based on severity and include age-adjusted serum creatinine, cardiac dysrhythmias, and seizures.⁴

How TLS happens

In a highly proliferative cancer such as acute leukemia, some leukemia cells die before treatment as part of their life cycle. If many of them

lyse and die, TLS may develop before cancer treatment even begins. However, most cancer cells in the bloodstream and bone marrow of patients with acute leukemia are destroyed with chemotherapy.

As cells lyse and die, they release intracellular components into the bloodstream. Large amounts of potassium and phosphate are released, along with purine nucleic acids.

Signs and symptoms of TLS may occur as early as a few hours after the start of chemotherapy, but it's more common 24 to 48 hours after treatment begins.⁵ The mortality rate for patients who develop TLS is about 18%.⁶ (See *Recognizing signs and symptoms of TLS*.)

What's going wrong?

Hyperkalemia is often a first sign of TLS because potassium may start to leave dying cancer cells before they lyse. This electrolyte imbalance can impair normal cardiac function and cause lethal dysrhythmias. The kidneys, overwhelmed by excess potassium in the bloodstream, may be unable to excrete enough potassium to compensate for the hyperkalemia.⁷

Hyperphosphatemia results from the large amount of phosphorus released from malignant cells, especially malignant blood cells.⁸ The kidneys try to eliminate the excess phosphorus by increasing urine output and reducing the amount of phosphorus reabsorption. But eventually the kidneys reach a point where they can no

longer compensate, and phosphorus accumulates in the blood.⁴

As serum phosphate levels increase, phosphate ions (which are negatively charged) combine with calcium ions (which are positively charged), resulting in decreased serum calcium levels (**hypocalcemia**). These calcium-phosphate complexes precipitate in soft tissues and the renal tubules, causing tubular obstruction and acute renal failure.⁵ Hyperphosphatemia usually develops 24 to 48 hours after the start of chemotherapy.⁸

Purine nucleic acids are also released by lysed cancer cells. Normally, purines are metabolized to hypoxanthine, which is converted to xanthine by the enzyme xanthine oxidase, and then to uric acid, which is excreted by the

Recognizing signs and symptoms of TLS^{1,5,7}

	Cardiovascular	Musculoskeletal	Neurologic	Gastrointestinal	Other
Hyperkalemia	<ul style="list-style-type: none"> • wide QRS complex • peaked T waves • dysrhythmias • hypotension • sudden death 	<ul style="list-style-type: none"> • muscle cramps • muscle weakness 	<ul style="list-style-type: none"> • paresthesia • paralysis 	<ul style="list-style-type: none"> • anorexia • nausea • vomiting • diarrhea • hyperactive bowel sounds • abdominal pain or cramps 	
Hyperphosphatemia	<ul style="list-style-type: none"> • dysrhythmias • hypertension 	<ul style="list-style-type: none"> • muscle cramps 	<ul style="list-style-type: none"> • seizures • tetany • lethargy 	<ul style="list-style-type: none"> • nausea • vomiting • diarrhea 	<ul style="list-style-type: none"> • calcium phosphate precipitates • acute renal failure • edema
Hyperuricemia	<ul style="list-style-type: none"> • hypertension • endocarditis 	<ul style="list-style-type: none"> • gout 	<ul style="list-style-type: none"> • lethargy • malaise • somnolence • seizures 	<ul style="list-style-type: none"> • anorexia • nausea • vomiting • diarrhea 	<ul style="list-style-type: none"> • acute renal failure • weight gain • edema • flank pain • hematuria • cloudy urine
Hypocalcemia	<ul style="list-style-type: none"> • dysrhythmia • hypotension • syncope 	<ul style="list-style-type: none"> • muscle spasms • muscle cramps • positive Chvostek and Trousseau signs 	<ul style="list-style-type: none"> • paresthesia • tetany • change in mental status • confusion • delirium • hallucinations • seizures (rarely) 	<ul style="list-style-type: none"> • anorexia • diarrhea • abdominal cramps 	<ul style="list-style-type: none"> • laryngospasm • bronchospasm

kidneys.⁴ Excess amounts of purine nucleic acids are released quickly into the bloodstream during cancer cell lysis, overwhelming the kidneys' ability to excrete the converted excess amounts of uric acid. This results in hyperuricemia and uric acid crystal formation in the kidneys.⁴

Because of these events, the kidneys are overwhelmed by excess potassium, phosphorus, calcium phosphate precipitates, and uric acid crystals, resulting in acute renal failure. Initially, the kidneys try to compensate for the increased electrolyte and uric acid load by increasing urine output, but they can't maintain normal electrolyte and uric acid levels due to volume depletion and uric acid nephropathy.⁵ Hyperuricemia is usually seen 48 to 72 hours after chemotherapy begins.⁸

If a patient is at risk for TLS, lab work is performed every 6 hours for the first 24 hours after chemotherapy is started. Lab work consists of a complete blood cell count, serum electrolytes, calcium, phosphorus, creatinine, uric acid, lactate dehydrogenase, and blood urea nitrogen (BUN). After the first 24 hours, lab values are monitored at least every 12 hours for several days and then daily, or as ordered. The severity of the patient's risk for TLS helps guide the frequency of lab work.⁹

Preventing and treating TLS

To help prevent TLS, assess patients undergoing chemotherapy for risk factors at baseline and monitor them during and after the initiation of treatment as ordered.¹ Mainstays of preventive care are hydration and the medications allopurinol and recombinant urate oxidase (rasburicase). Alkalinization of the urine, once a common treatment for TLS, is no longer routinely recommended. (See *Urinary alkalinization: Out of favor?*)

I.V. hydration should begin as soon as possible, ideally 2 days

before initiating chemotherapy, and continue during chemotherapy and for 2 to 3 days afterward.⁵ The optimal fluid volume administered parenterally is 3,000 mL/m² each day. This will produce the high urine output (over 100 mL/m² each hour) that's needed to excrete excess potassium, phosphate, and uric acid, with the goal of reducing the risk of calcium phosphate precipitates.⁷ Electrolytes, such as potassium, aren't added to I.V. fluids to avoid the risk of worsening electrolyte abnormalities.

Monitor the patient for signs and symptoms of fluid volume overload, such as peripheral edema, neck vein distension, weight gain, and pulmonary crackles, as well as signs and symptoms of fluid volume deficit (dehydration), such as dry mucous membranes, poor skin turgor, weight loss, and thirst. Use physical assessment, strict intake and output, daily weights, and lab work results to monitor renal function, including serum creatinine and BUN levels, and calcium, phosphate, potassium, and uric acid levels. In some cases, the healthcare provider may order a diuretic such as furosemide to enhance renal excretion, but diuretics should be avoided in patients who are dehydrated or who have renal obstruction.^{1,4}

Allopurinol inhibits the conversion of hypoxanthine to xanthine and of xanthine to uric acid by inhibiting xanthine oxidase. Optimally, it's initiated 1 to 2 days before starting chemotherapy.¹ Monitor patients for a skin rash or fever, which may indicate a hypersensitivity reaction. Other signs and symptoms of a hypersensitivity reaction include chills, nausea, vomiting, and a high serum eosinophil count. Common adverse reactions from allopurinol include central nervous system alterations, such as drowsiness or headache.

Allopurinol therapy is started before chemotherapy because it

Urinary alkalinization: Out of favor?

Historically a mainstay of TLS prevention, the use of I.V. sodium bicarbonate to alkalinize the urine has become controversial. Adding sodium bicarbonate to I.V. fluids raises the patient's urine pH above 7, increasing excretion of uric acid.⁵ When the uric acid level returns to normal, alkalinization is stopped. However, an alkaline environment can promote calcium and phosphorus precipitation and promote renal failure, as well as metabolic alkalosis. When used with allopurinol, alkalinization can also interfere with xanthine and hypoxanthine solubility and promote urinary xanthine crystal deposits in the kidneys. For these reasons, routine alkalinization is no longer recommended, although some practitioners still order it.¹

helps prevent excess uric acid, but it won't reduce uric acid levels in patients who already have hyperuricemia. Another limitation of allopurinol is that it increases xanthine levels, which could precipitate in the kidneys. In addition, it interferes with the excretion of other drugs used to treat cancer, such as high-dose methotrexate, cyclophosphamide, e-mercaptopurine, and azathioprine.¹ Allopurinol is never administered with capecitabine because allopurinol may decrease its effectiveness.

Unlike allopurinol, rasburicase is a drug that treats hyperuricemia. Administered I.V., rasburicase converts uric acid to allantoin, which is much more soluble in urine than uric acid. The drug works quickly (in 4 hours) to reduce uric acid levels and also helps control serum potassium, phosphate, calcium, and creatinine levels.¹⁰ Most patients receive 2 days of therapy, but just one treatment is effective for some. Patients with a large tumor burden may need longer therapy (up to 7 days) or twice-daily treatment.^{1,10}

If you care for a patient taking rasburicase, take special care when

sending lab specimens for uric acid analysis. To ensure accurate uric acid results, the blood specimen must be placed on ice after being drawn, during transport, and while in the lab waiting to be processed. Improperly obtained and maintained specimens will give abnormal false low results due to any uric acid in the tube being degraded by rasburicase at room temperature.

Allopurinol must be stopped in patients who are to receive rasburicase. Never use the two drugs together because allopurinol will interfere with rasburicase activity. Make sure the patient is well hydrated before administering rasburicase therapy.¹⁰

Because of the risk of a hypersensitivity reaction, make sure emergency medications (such as oxygen, epinephrine, corticosteroids, and diphenhydramine) are available before rasburicase therapy begins. Take baseline vital signs and closely monitor the patient throughout drug administration. Signs of hypersensitivity reactions include urticaria, bronchospasm, chest discomfort, dyspnea, hypoxia, and hypotension. Stop the

rasburicase infusion at the first sign of a hypersensitivity reaction, assess and maintain airway, breathing, and circulation, obtain vital signs, notify the healthcare provider, administer treatment as ordered, and support the patient during the reaction.

Headache, rash, fever, and vomiting are the most common adverse reactions associated with one dose of rasburicase. With repeated dosing, additional adverse reactions include increased liver enzymes, urticaria, pruritus, flushing, dyspnea, and chest and back pain.¹¹ Hemolysis, hemoglobinuria, and methemoglobinemia have been reported. Rasburicase should never be administered to patients with a glucose-6-phosphate dehydrogenase deficiency because of the risk of severe hemolysis.

Treating complications of TLS

A patient who develops TLS requires ongoing hydration. Asymptomatic hyperkalemia is managed with sodium polystyrene sulfonate with sorbitol given orally. Monitor the patient for signs and symptoms of hypocalcemia and hypomagnesemia from sodium polystyrene sulfonate with sorbitol.¹⁰ Also monitor the patient's 12-lead ECG as indicated and assess cardiac rate and rhythm for dysrhythmias.

If the patient has symptomatic hyperkalemia, the healthcare provider may order I.V. regular insulin and dextrose to redistribute potassium, shifting it intracellularly.^{4,10} I.V. calcium chloride may be ordered to control dysrhythmias by antagonizing the toxic effects of hyperkalemia at the cardiac cellular membrane level and manage hypocalcemia.^{1,10} However, I.V. calcium shouldn't be administered to patients with hyperphosphatemia because it promotes calcium phosphate precipitates.⁴

Hyperphosphatemia is managed with phosphate binders such as aluminum hydroxide given in lim-

ited dosages to avoid aluminum toxicity.¹ Other phosphate binders with calcium, such as calcium acetate or calcium carbonate, may be used instead.¹² A patient who doesn't respond to these measures may need renal replacement therapy, such as hemodialysis, to manage electrolyte abnormalities and treat renal failure.

Nursing considerations

Educate patients and their families about the prevention and management of TLS, including the signs and symptoms of hyperuricemia and information about prescribed medications. For example, make sure they understand each drug's purpose, dosage, expected effects, and possible adverse reactions. Also make sure they know how to recognize serious adverse reactions or signs and symptoms they should notify the healthcare provider about at once.

Complete a nursing admission assessment, including a risk factor assessment for TLS. Notify the healthcare provider of any abnormal lab results that may indicate TLS.

Administer I.V. hydration as prescribed and monitor fluid balance by weighing the patient daily and documenting intake and output accurately. Urine output should be in balance with the intake. If fluid intake exceeds output, notify the healthcare provider because the patient may be developing renal complications from TLS.

To assess a patient's renal function, follow these guidelines.

- Assess urine output, including pH, color, odor, volume, and clarity, and test for the presence of red blood cells and hemoglobin. Notify the healthcare provider of oliguria or other abnormalities, which may indicate acute renal failure. Educate the patient about the need to save all urine for measurement and testing.
- Insert an indwelling urinary catheter if prescribed, but avoid

Beware of these medications⁹

This is a partial list of medications to avoid in patients with TLS.

- angiotensin-converting enzyme inhibitors
- antifungals
- aspirin
- beta-blockers
- bisphosphonates
- cyclosporine
- heparin
- mannitol
- some antineoplastics
- some antibiotics
- potassium-sparing diuretics
- medications containing potassium or phosphate
- nephrotoxic agents such as non-steroidal anti-inflammatory drugs and aminoglycosides

catheters in patients with low neutrophil or platelet counts due to the risk of infection and bleeding, and remove urinary catheters as soon as they're no longer needed to prevent catheter-associated urinary tract infections.

- Assess breath sounds (pulmonary crackles) and heart sounds (S₃) for signs of fluid overload.
- Weigh the patient daily.
- Monitor BUN, serum uric acid and creatinine levels.
- Perform medication reconciliation and collaborate with the prescriber and pharmacist to stop or hold any medications that may adversely affect renal function or serum electrolyte and uric acid levels. (See *Beware of these medications.*)

To assess a patient for signs and symptoms of hyperkalemia, hyperphosphatemia, and hypocalcemia, closely monitor electrolyte, phosphorus, and calcium levels, and monitor ECG results. As pre-

scribed, administer phosphate binding agents, medications to reduce serum potassium and uric acid levels, and increase serum calcium levels.

Prompt recognition is key

By promptly identifying signs and symptoms of TLS and intervening appropriately, you can help your patient recover from this dangerous complication of cancer treatment. ■

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Jeanne Held-Warmkessel is a clinical nurse specialist at Fox Chase Cancer Center in Philadelphia, Pa.

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